

REQUEST FOR RECONSIDERATION

Clinically, recombinant human growth hormone (rhGH) is administered daily in growth hormone deficient patients. To decrease the dosing frequency and increase patient compliance sustained release formulations have been under development. These formulations have the potential to allow patients to decrease their dosing interval from daily to once or twice per month. The present invention addresses the release profile of sustained release formulations.

The present invention includes a sustained release composition including a carrier material containing a non-polymeric, non-water soluble liquid material having a viscosity of at least 5,000 cP at 37°C that does not crystallize neat under ambient physiological conditions, multivalent metal cations and growth hormone. This composition provides a very low burst of from 0.1 to 2.2% in 24 hours, followed by protein release over 28 days. A comparative composition, identical except for substitution of sodium bicarbonate for multivalent metal cations, gives a much higher initial burst, 7-14% in 24 hours.

The rejection of Claims 1 and 26-30 under 35 U.S.C. § 102 over European Patent Application 0 216 485 (EP '485) is respectfully traversed. None of the components used in the oil vehicles of EP '485, nor the oil vehicle itself, is a liquid material having a viscosity of at least 5,000 cP at 37°C.

EP '485 describes prolonged release of growth promoting hormones. This reference describes an oil vehicle together with an effective amount of a metal complex of a growth promoting hormone (page 2, lines 12-14). The oil vehicle is composed of 90-99% oil, and 1-10% of known adjuvants or excipients (page 4, lines 6-17). The oils include a variety of vegetable and mineral oils (page 3, line 35 to page 4, line 2). The adjuvants and excipients include beeswax, aluminum monostearate, carnauba, and paraffin (page 4, lines 11-15). These compositions are administered via injection or implants containing a pump or matrix (page 5, lines 22-35).

The present invention includes a liquid material having a viscosity of at least 5,000 cP at 37°C. The oils of the oil vehicle of EP '485 have viscosities far low than 5,000 cP at 37°C (see the attached page from "HANDBOOK OF CHEMISTRY AND PHYSICS", page 6-159, showing that the viscosity of olive oil and soybean oil to be less

than 100 cP at 20°C). The adjuvants and excipients of EP '485 are all solids. Finally, the mixture of the adjuvants or excipients, and the oils, are *injectable* compositions, and therefore must have relatively low viscosities. (Please note that the present invention includes a solvent with the liquid material having a viscosity of at least 5,000 cP at 37°C, in the examples where the composition is injected; Tipton et al. at column 6, lines 20-28, describes some of the unusual viscosity properties SAIB, a member of this class of liquid materials). Finally, there is no suggestion in EP '485 to use a liquid material having a viscosity of at least 5,000 cP at 37°C. Applicants submit that the claimed invention is neither anticipated by, nor obvious over, EP '485 alone.

The rejection of the claims under 35 U.S.C. § 103 over European Patent Application 0 216 485 (EP '485) in view of Tipton, et al. is respectfully traversed. The claimed invention provides for an initial burst which is about ten times smaller than comparative compositions which do not contain multivalent metal cations, a much lower initial burst than would have been expected based on the teachings of EP '485. These unexpected and superior results demonstrate the unobviousness of the claimed invention.

EP '485 is described above. Example 5 is the only example which compares the release rates of compositions which are identical except for the presence of multivalent metal cations (pages 10-14). In this example, compound 1 contains peanut oil, 5% aluminum monostearate and 8 mg/ml of uncomplexed Parlow swine growth hormone; formulation 3 contains peanut oil, 5% aluminum monostearate and 8 mg/ml of zinc complexed growth hormone (page 10, lines 23-31). Tables 4 and 5 (pages 12 and 13) show the serum growth hormone levels for administration of the two compositions over a period of time. The earliest point in time after administration of the growth hormone for which both examples have data is at the 24 hour mark: serum growth hormone was 84.6 ng/ml for the uncomplexed growth hormone, and 40.0 ng/ml for the complexed growth hormone. This shows a decrease in the amount released of about 50% when multivalent metal cations are present. This is consistent with the 200% increase in release time of the growth hormone as concluded by this reference (page 14, lines 13-18).

Tipton et al. has been cited for a description of SAIB. There is no discussion of changes in release rates of growth hormone from the presence or absence of multivalent metal cations.

The claimed invention shows a greater than 10 fold drop in amount of growth hormone released within the first 24 hours, as compared to compositions without multivalent metal cations. Figure 4 includes release rate data for comparable compositions which either contain multivalent metal cations, or sodium bicarbonate (this experiment is described in the specification, page 6, lines 11-25). In the ethanol containing composition, 0.53% of the multivalent metal cation containing composition was released in 24 hours, while the otherwise identical sodium bicarbonate composition released 6.53% over 24 hours. In the benzyl benzoate containing composition, 1.06% of the multivalent metal cation containing composition was released within 24 hours, while the sodium bicarbonate composition released 14.64% over 24 hours. This data indicates that the initial burst within 24 hours is reduced more than 10 fold when multivalent metal cations are present. Since EP '485 at best suggests a 2 fold decrease in initial burst within 24 hours, the present invention provides unexpected and superior results. Accordingly, Applicant submits that this data demonstrates the unobviousness of the claimed invention.

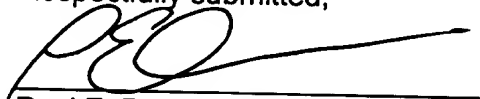
The objection to the drawings has been obviated by the filing herewith of formal drawings. Withdrawal of this objection is respectfully requested.

The objection to the abstract has been obviated by appropriate amendment.

The claim to priority has been corrected.

Applicant submits the application is now in condition for allowance. Early notice of such action is earnestly solicited.

Respectfully submitted,

A handwritten signature in black ink, appearing to read 'P. E. Rauch', written over a horizontal line.

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HANDBOOK
of
CHEMISTRY
and
PHYSICS

DAVID R. LIDE
Editor-in-Chief

72ND
EDITION
1991 — 1992

VISCOSITY OF LIQUIDS (Continued)

Temp. °C	Viscosity cp	Liquid	Temp. °C	Viscosity cp	Liquid	Temp. °C	Viscosity cp
15	2.88		40	1.00	n-Propyl alcohol.....	0	3.833
30	1.77		60	1.18		15	2.62
25	3.57		60	1.20		20	2.258
25	3.331		20	.711		30	1.72
50	2.68		0	.706		40	1.405
100	2.32		15	.574	n-Propyl alcohol.....	50	1.130
141	2.118		20	.542		70	.760
500	1.54		40	.433	Propyl aldehyde.....	10	.47
551	1.70		40	2.88		20	.41
600	1.38		15	10.6		40	.33
703	1.349		10	2,420	bromide.....	0	.851
844	1.185		20	.086		20	.524
55.6	0.20		30	.461		40	.433
74.8	2.47		40	.231	chloride.....	0	.426
90.0	1.04		100	16.9		20	.352
-20	1.855		20	70.4		40	.291
-10	1.764		37.8	240.6	n-Propyl ether.....	15	.448
0	1.685		100	18.7	Pyridine.....	20	.074
10	1.615		37.8	422.4	Salicylic acid.....	10	3.20
19.02	1.56		100	24.0		20	2.71
20	1.554		30	33.1		40	1.81
20.2	1.55		50	17.6	Salol.....	45	.746
30	1.499		90	7.1	Sodium bromide.....	762	1.42
40	1.450		15.6	113.8		760	1.28
40.8	1.45		37.8	34.2	chloride, liq.....	841	1.20
41.86	1.44		100	4.9		896	1.01
50	1.407		15.6	680.6	nitrate, liq.....	924	.97
60	1.367		37.8	127.4		308	2.919
70	1.331		10	138.0		348	2.439
80	1.298		20	84.0		398	1.977
90	1.268		40	38.3		413	1.828
100	1.240		70	12.4	Stearic acid.....	70	11.0
150	1.130		0	2,630	Sucrose (cane sugar).....	109	2.8 x 10 ⁴
200	1.032		10	285		124.8	1.9 x 10 ⁴
250	.905		20	183	Sulfur (gas free).....	123.0	10.94
300	.850		30	96		135.5	8.66
340	.921		20	69.3		142.5	7.09
0	.484		30	40.6		156.3	7.19
20	.381		50	20.6		158.2	7.59
40	.320		90	7.8		159.2	5.48
-08.40	13.9		15.6	42.0		159.5	14.45
-84.23	6.8		37.8	18.5		160.0	22.83
-72.52	4.36		100.0	4.6		160.3	77.32
-44.63	1.98		30	25.6		165.0	500.0
-22.29	1.23		22	2.81		171.0	4,500.0
0	.82		0	.289		184.0	10,000.00
15	.872		20	.240		190.5	19,700.0
20	.897		0	18.5		197.5	21,800.0
25	.947		20	6.08		200.0	21,500.0
30	.910		30	4.22		210.0	20,500.0
40	.856		30	12.9		217.0	19,100.0
50	.803		20	12.9		220.0	18,000.0
0	.236		20	8.3	Sulfur dioxide, liq.....	-33.5	.5508
25	2.02		18.3	12.7		-10.5	.4285
30	1.55		50	3.49		0.1	.3936
20	.1834		60	2.61	Sulfuric acid.....	0	48.4
15	1.09		70	2.03		15	32.8
30	0.92		90	1.26		20	26.4
15	.449		.28	1.96		30	15.7
30	.303		20.0	1.35		40	11.5
0	.606		21.5	2.34	Sulfuric acid.....	50	8.82
15	.518		31.2	3.01		60	7.23
20	.500		43.2	1.73		70	6.09
20	.460		50.5	1.60		80	5.19
40	.424		60.3	1.45	Tetrachloroethane.....	15	1.844
80	.967		69.7	1.32	Tetradecane.....	20	2.18
100	.776		79.9	1.21	Tin, liq.....	240	3.12
0	2.215		745	1.48		280	1.678
10	1.770		775	1.34		300	1.73
2.93	2.91		805	1.10		301	1.680
5.69	2.71		334	2.1		400	1.43
6.94	2.45		868	1.7		450	1.270
9.92	2.24		333	2.97		500	1.20
14.04	2.03		418	2.00		600	1.08
20.00	.852		10	1.289		604	1.045
0	.620		15	1.18		750	.905
25	1.84		20	1.102	Toluene.....	0	.772
0	4.37		40	.845		17	.61
20	1.03		10	.68		20	.600
40	1.21		20	.59		30	.528
60	2.33		40	.44		40	.471